vaccine annually, and hepatitis B vaccine if results of the hepatitis panel are negative.

The only anti-HIV therapy that is approved by the Food and Drug Administration at this time is zidovudine (AZT). This nucleoside analogue selectively inhibits HIV type 1 reverse transcriptase activity and viral replication. Two recent clinical trials have shown that the development of AIDS or severe AIDS-related complex is substantially delayed in patients taking AZT. In addition, the use of AZT has been shown to have significant therapeutic effects in patients with AIDS dementia. It is generally recommended to begin AZT therapy in all HIV-infected patients with CD4 counts of less than 0.5 cells $\times 10^9$ per liter (500 cells per μl). Some argue that this increases the risk of drug resistance developing, however. Recent clinical trials have shown that decreasing the dose from 1,500 mg per day to 500 mg per day (100 mg every four hours) offered asymptomatic patients clinical benefit with substantially fewer toxic effects. Another dideoxynucleoside analogue, dideoxyinosine (DDI), is presently undergoing a clinical stage II-III trial. Studies show it has potent anti-HIV activity, but it also has significant toxicity, some of its effects including peripheral neuropathy and pancreatitis.

The US Public Health Service recommends *Pneumocystis carinii* pneumonia prophylaxis for all patients with CD4 counts of less than 0.2 $\times 10^9$ per liter (200 per μl). The combination drug, trimethoprim-sulfamethoxazole, 5 mg per kilogram per day in a divided dose for three days a week, is one regimen. Unfortunately, there is a relatively high incidence of sulfa sensitivity in patients with AIDS. The use of dapsone, 50 mg per day, is an acceptable alternative that has not been studied as carefully. Aerosolized pentamidine given as a 300-mg dose every month was shown to decrease the number of episodes of *P carinii* pneumonia and prolong survival. There have been a few reports of extrapulmonary *P carinii* in patients receiving aerosolized pentamidine treatments. Pulmonary relapses in this population tend to be in the upper lobes.

Mycobacteria, both typical and atypical forms, have a strong association with HIV infection. The Centers for Disease Control recommend that any HIV-positive person, regardless of age, who has a positive PPD skin test (5 mm of induration) take isoniazid, 300 mg per day, for about a year. Currently there is no accepted prophylactic regimen for atypical mycobacteria.

Recurrent herpes simplex virus 1 and 2 and herpes zoster infections can be prevented with the use of acyclovir, 200 mg three to four times a day. The routine use of acyclovir or ganciclovir in an effort to prevent symptomatic cytomegalovirus infection is not recommended.

Persons infected with HIV who have a positive RPR or VDRL should have a lumbar puncture study done. If the cerebrospinal fluid (CSF) is normal, the patient may be treated with 2.4 million units of penicillin G benzathine given intramuscularly weekly for three weeks. If there are typical symptoms of neurosyphilis or if the CSF VDRL is positive for syphilis, treatment should be started. Many HIV-infected persons have an increased CSF protein concentration and pleocytosis, so these findings alone do not implicate neurosyphilis.

Human immunodeficiency virus disease should be considered a progressive, chronic process. Primary care practitioners need to lay the foundation for the care of HIV-positive patients. Patients can manifest a spectrum of diseases, many of which may now be preventable. Checking serial CD4 counts and getting careful interval histories and physical examinations will enable physicians or allied health care practitioners to stage the disease and plan appropriate maintenance measures.

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Harmful Health Effects of Passive Smoking

ALTHOUGH THE ROLE of direct cigarette smoking in chronic diseases including lung cancer and heart disease has been well established, scientific evidence has only recently implicated the indirect inhalation of cigarette smoke as a risk factor for disease as well. Since the Surgeon General's 1986 report on involuntary smoking, several hundred scientific articles have reported the harmful effects of environmental tobacco smoke. The Environmental Protection Agency recently called environmental tobacco smoke "one of the most widespread and harmful indoor air pollutants."

The strongest evidence linking passive smoking to increased disease prevalence exists in children. Even in temperate climates, children spend about two thirds of their time indoors, placing family members living with smokers at increased risk. It is estimated that 70% of all children in the United States are exposed to the hazards of cigarette smoke for much of their developmental years. During the first year of life, pneumonia and bronchitis appear with greater frequency in infants with exposure to cigarette smoke. There is also an increased incidence of otitis media, bronchitis, acute exacerbations of asthma, and reduced lung function in children whose parents smoke. Cough and mucus production occur more frequently among children of smokers. These clinical problems often have a dose-response relationship whereby the more cigarettes per day the parents smoke, the more likely a child is, for example, to require asthma medications. In addition, an increased serum immunoglobulin E level and an increased prevalence of eosinophilia have been seen among children of smoking parents. This may explain in part the increased frequency of respiratory symptoms in children of smoking parents. Furthermore, children whose parents smoke are twice as likely to become smokers themselves, additionally jeopardizing their health in later life.

The risk of environmental tobacco smoke to adults has not been examined extensively and is therefore not conclusive. One startling finding is that passive smoking is associated with a higher risk of lung cancer in nonsmokers. The National Academy of Sciences (1986) estimated that 3,800 lung cancer deaths each year in the United States are caused by passive smoking. Studies examining respiratory symptoms in adults with exposure to secondhand smoke have shown conflicting results, as have others examining lung function and clinical exacerbations of asthma. Those living with smokers are not the only ones at risk. A health insurance survey concluded that almost two thirds of nonsmoking adults had

some exposure to passive smoke, most often in places outside the home. Testing for urinary or salivary levels of cotinine, a by-product of cigarette smoke, has documented the presence of tobacco smoke exposure in a large proportion of the general population.

Secondhand smoke is now recognized as a health threat in this country. This has caused a dramatic change in public attitudes regarding the rights of the smoking minority versus the welfare of the nonsmoking public. Further research is needed to determine more precisely how great the risk is from this exposure.

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Immunoglobulin G Subclasses

THE FOUR IMMUNOGLOBULIN (Ig) G subclasses are products of discrete constant region genes encoded within the immunoglobulin heavy-chain locus on chromosome 14. Each immunoglobulin represents the expression of several rearranged variable region genes with one constant region gene producing a single polypeptide chain. The finished immunoglobulin molecule is a four-chain structure composed of two identical heavy chains coupled to two identical light chains (κ or λ) encoded on chromosomes 2 and 22, respectively. Monoclonal antibody and recombinant genetic technology have resulted in major advances in understanding immunoglobulin structure-function relationships as well as accurate methods for measuring IgG subclasses and specific antibodies to defined antigens.

Studies of purified isolates of human IgG subclasses, or genetically constructed antibodies of identical variable regions (idiotype) but different constant regions (isotype), have supplemented and clarified earlier studies of naturally occurring antibodies. These studies confirm major effector differences in IgG subclass antibodies. IgG3 is more efficient than IgG1 in activating complement, but IgG2 is minimally active and IgG4 is inactive. IgG1 is more efficient than IgG2 in enhancing human complement-mediated killing of some bacterial pathogens. IgG4 is functionally univalent and does not form large latticed immune complexes. Although these differences may have clinical implications, extrapolation from in vitro studies to defense capabilities in vivo may be misleading because of the physiologic redundancy of defense mechanisms.

Minor IgG subclass deficiencies have been linked to an increased susceptibility to infection. Often IgG2 or IgG2 to IgG4 deficiency occurs along with IgA deficiency. The strongest disease association has been that of low IgG2 levels and recurrent infection with encapsulated bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. The clinical implications of low IgG subclass levels are not well understood, however. Healthy persons lacking constant region genes for one or more IgG subclasses have been identified; healthy blood donors with variable IgG subclass deficiencies have also been found; persons with initially low IgG subclass levels can correct over time; and, finally, normal IgG subclass levels but deficient specific antibody responses have been described in persons with recurrent infection. Thus, IgG subclass deficiencies are likely markers of broader immune abnormalities rather than inherent causes of disease. The best understood example of this is also IgG2 deficiency. Low IgG2 levels in patients with recurrent infection are associated with an inability to respond to bacterial polysaccharides, but in healthy IgG2-deficient persons, normal antibody responses are seen. This suggests that the primary defect is specific immune responsiveness to bacterial polysaccharides; if impaired, low IgG2 levels are frequently but not invariably found. Therefore, the assessment of recurrent sinopulmonary or systemic pyogenic infection—the major indication for evaluating IgG subclasses—should include both IgG subclass levels and specific antibody responses to protein and polysaccharide antigens, including the paired measurement of serum before and four weeks after immunization with capsular vaccines such as unconjugated *H influenzae* type b and pneumococcal polysaccharide vaccine. Age-related interpretation is essential because healthy infants and toddlers may not respond to these vaccines. At present, IgG subclass-specific antibody assays are not generally available. An IgG subclass deficiency associated with impaired antibody responses can be treated with intravenous immune globulin if conservative measures such as antibiotic prophylaxis are ineffective. The use of intravenous immune globulin therapy in patients with an IgG subclass deficiency without a demonstrably impaired antibody response is controversial; many clinicians await the results of a multicenter controlled trial now in progress.

An analysis of IgG subclass levels must take into account their non-Gaussian distribution, wide normal ranges, and ethnic differences. Allelic population differences in certain heavy- and light-chain regions (allotypes) can affect IgG subclass levels and specific antibody responses. For example, whites with the IgG2m(n) allotype have higher IgG2 levels and antibody responses to bacterial polysaccharides than persons lacking this allele. Adult levels of IgG1 and IgG3 are attained earlier than levels of IgG2 and IgG4. For IgG3 and especially for IgG4, true deficiencies are hard to establish, given that low levels are found in many normal younger children.

Generally, antibody responses to protein antigens—such as viral envelopes—mainly involve IgG1 and IgG3. Antibody responses to capsular polysaccharides seem to fall into two groups, those eliciting greater IgG2 isotype restriction such as *S pneumoniae* and those with a lesser degree of IgG2 restriction such as *H influenzae* or meningococcal types A and C, where substantial IgG1 responses may occur. Finally, antibody responses to protein antigens presented repetitively, such as allergen extracts used in hyposensitization therapy, are largely restricted to IgG1 and IgG4, with the latter often predominant.

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